REMARKS

The specification page 18 line 8 through page 19 line 17, and Claims 12 and 29 have been amended to correct the tetravalent nitrogen atoms in the substituents: $-NR^dH-C(=NH)-NH_2$ and $-NHR^aR^b$, to read as trivalent nitrogen atoms as follows: $-NR^d-C(=NH)-NH_2$ and $-NHNR^aR^b$.

These were clearly meant to read as $NR^d-C(=NH)-NH_2$ and $-NHNR^aR^b$ as the other alternative trivalent substituents: $-NH-C(=NH)-NH_2$ and $-N(R^aR^b)$ were already present in the list of substituents. No new matter is being added as a result of this amendment.

The remaining amendments to the claims are discussed in detail below.

Claim Rejection under 35 USC § 112 first paragraph

1. Claims 1-35 are rejected under 35 USC § 112 first paragraph, because the Examiner asserts that the specification is not enabling for all forms of cancer which are multi-drug resistant.

The instant specification, Examples 1-14, teaches how to make over one hundred species within the claimed genus. See MPEP 2164.01(b):

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims, then the enablement requirement of 35 U.S.C. 112 is satisfied.

Cancers which can be treated by the methods of the invention are taught in the instant specification page 20 line 25 through page 22 line 25. Methods of administration and suitable dosage amounts are taught page 23 line 10 through page 24 line 2. See MPEP 2164.01(c):

> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied.

Further, the instant specification provides working examples which demonstrate the biological efficacy of these compounds against **three distinct** types of multi-drug resistant

cancers (Examples 15-17). Examples 15-17 show that compounds **(1)-(18)** treat a variety of very different multi-drug resistant cancer types, such as, blood-borne cancers e.g., leukemia and solid tumors, e.g., sarcomas and melanomas. The law does not require a patent application to exemplify every species in a genus, in order to show enablement of that genus, see MPEP 2164.02:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.

nor does the law require them to demonstrate the operability of every species within the claimed genus, see *Amgen, Inc. v. Chugai Pharm. Co., Ltd.,* 927 F.2d 1200 at 1213 (Fed. Cir. 1991):

> Moreover, it is not necessary that a patent applicant test all the embodiments of his invention, *In re Angstadt,* 537, F.2d 498, 502, 190 USPQ 214, 218 (CCPA 1976); what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims.

Moreover, fulfillment of the requirements of 35 U.S.C, § 112 first paragraph does not require that the skilled artisan be able to predict, with certainty, that every embodiment of the claimed invention would be functional. Under 35 USC § 112 first paragraph the application must explain how to "make and use" the claimed invention. The courts have interpreted this statute to mean that the specification must teach the skilled artisan how to practice the invention without undue experimentation. Thus the test is not whether experimentation is necessary, but whether any experimentation would be undue in view of what type and amount of experimentation is typical in the area. See *In re Wands,* 858 F.2d 731 at 736- 737

> Enablement is not precluded by the necessity for some experimentation such as routine screening.

See also MPEP 2164.01

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

The Applicants have provided representative examples of how to make and use the compounds to treat a number of distinct types of multi-drug resistant cancers. Methods of screening drugs to ascertain their efficacy in treating certain related diseases is standard in the pharmaceutical art, and therefore could not be considered undue. Therefore, one of skill in the art would be able to practice the invention within the scope of the claims without undue experimentation, and the enablement requirement of 35 U.S.C, § 112 first paragraph is satisfied. Withdrawal of the rejection is respectfully requested.

Further, Claims 18-29 and 35 are directed to treatment of cancers (including multi-drug resistant cancers) comprising administering the compound described therein alone or in combination with an anti-cancer drug other than a taxol analog. The instant specification provides working examples which demonstrate the biological efficacy of these compounds in treating a subject with non-multi-drug resistant cancers including both blood-borne cancers and solid-tumors, **alone** and **in combination with anti-cancer drugs other than a taxol analog**. Firstly, Example 19 demonstrates that compound (**1**) alone shows similar anti-cancer activity to commonly used anti-cancer drugs Vincristin and A taxol analog for **seven different** types of leukemia cells. Secondly, Example 18 demonstrates that compound (**1**) also increases the anti-cancer activity of Epothilone D in human breast carcinoma cell lines. The combination of these two examples would indicate that:

1) the compounds are effective at treating both blood-borne and solid tumors, and
2) the compounds show anti-cancer activity:
    a. when administered alone, and
    b. when administered in combination with a second anti-cancer drug other than a taxol analog.

Applicants have therefore provided representative examples of how to make and use the compounds with the generic methods of the instant claims and one of skill in the art would be able to practice the invention within the scope of the claims. Therefore the enablement requirement of 35 U.S.C. §112 first paragraph is satisfied, and withdrawal of the rejection is respectfully requested.

Claim Rejection under 35 USC § 112 second paragraph

2. The Examiner further rejects Claims 5-7, 13-17, 22-32 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that there is insufficient basis for the limitation "phenylene group" in the definition of the variable Y in Claims 5 and 22 or a "1,4 phenylene group" in the definition of the variable Y in Claim 23.

Claim 5 is dependent from Claim 2 which is dependent from Claim 1. Claims 22 and 23 are dependent from Claim 19 which is dependent from Claim 18. In Claims 1 and 18 Y is defined as:

> ...a substituted or unsubstituted hydrocarbyl group...

A hydrocarbyl group is defined page 16 lines 24 through page 17 lines 5 as:

> A "straight chained hydrocarbyl group" is an alkylene group i.e., $-(CH_2)_x-$, with one or more (preferably one) internal methylene groups optionally replaced with a linkage group. x is a positive integer (e.g., between 1 and about 10), preferably between 1 and about 6 and more preferably 1 or 2. A "linkage group" refers to a functional group which replaces a methylene in a straight chained hydrocarbyl. Examples of suitable linkage groups include a ketone (-C(O)-), alkene, alkyne, phenylene, ether (-O-), thioether (-S-), or amine [-N(R^a)]-, wherein R^a is defined below...

Therefore a straight chained hydrocarbyl group includes a phenylene group and there is sufficient antecedent basis in Claims 5, 22 and 23 for the term phenylene group. However to avoid duplication of terms in Claims 5 and 22 the term phenylene group has been deleted as it is already encompassed in the term hydrocarbyl group. Withdrawal of the rejection is respectfully requested.

The Examiner states that there is insufficient basis for the limitation "Y is ...-$C(R_7R_8)$-" in Claims 6, 7 and 24 and "Y is ...-CH_2CH_2-" in Claim 23.

Claim 6 is dependent from Claim 5. Claims 23 and 24 are dependent from Claim 19 which is dependent from Claim 18. In Claims 5 and 18 Y is defined as:

...a substituted or unsubstituted straight chained hydrocarbyl group...

$-CH_2CH_2-$ is an unsubstituted hydrocarbyl group, and $-C(R_7R_8)-$ is a hydrocarbyl group substituted with R_7 and R_8 groups. Therefore there is proper antecedent basis for these terms. Claim 7 is dependent from Claim 2 which is dependent from Claim 1. In Claim 1 Y is defined as:

...a substituted or unsubstituted straight chained hydrocarbyl group...

$-C(R_7R_8)-$ is a hydrocarbyl group substituted with R_7 and R_8 groups. Therefore Claims 7, 22 and 23 are properly dependent and there is antecedent basis for all the terms described therein. Withdrawal of the rejection is respectfully requested.

The Examiner states that there is insufficient basis for the limitation "unsubstituted aliphatic group" in the definition of R_1 and R_2 in Claims 13 and 30.

Claim 30 is dependent on Claim 14 which is dependent on Claim 13 which in turn is dependent from Claim 1. In Claim 1 R_1 and R_2 are defined as:

...an aliphatic group, a substituted aliphatic group...

In this instance the duplication of the term aliphatic group in the definition of $R_1 - R_4$ was clearly intended to cover substituted and unsubstituted aliphatic groups. Claim 1 has been amended to read "...an unsubstituted aliphatic group, a substituted aliphatic group..." . This amendment is being made for clarification purposes only, no narrowing of the claim is intended, nor is any new matter being added as a result of this amendment. In light of this Claims 13 and 30 are properly dependent and there is antecedent basis for all there terms described therein. Withdrawal of the rejection is respectfully requested.

The Examiner states that there is insufficient basis for the limitation "optionally substituted with at least one alkyl group" in the definition of R_1 and R_2 in Claims 14 and 31.

Claim 31 is dependent from Claim 30 which is dependent from Claim 14 which is dependent from Claim 13 which in turn is dependent from Claim 1. In Claim 1 R_1 and R_2 are defined as:

...a substituted aliphatic group...

An aliphatic group is defined in the specification page 17 lines 11 – 12 as:

> An aliphatic group is preferably a straight chained, branched or cyclic non-aromatic hydrocarbon...

Page 19 lines 18 – 19 reads:

> Preferred substituents for a cycloalkyl group, including cycloalkyl groups represented by R_1 and R_2, are alkyl groups, such as a methyl or ethyl group.

Therefore, there is antecedent basis for a cycloalkyl group optionally substituted with an alkyl group in Claims 14 and 31. Withdrawal of the rejection is respectfully requested.

The Examiner states that there is insufficient basis for the limitation "unsubstituted alkyl group" in the definition of R_3 and R_4 in Claims 15 and 32.

Claim 32 is dependent on Claim 31 which is dependent on Claim 30 which is dependent on Claim 14; Claim 15 is dependent from Claim 14 which in turn is dependent from Claim 1. In Claim 1, R_3 and R_4 are defined as:

...an aliphatic group, a substituted aliphatic group...

As discussed above Claim 1 has been amended to read "...an unsubstituted aliphatic group, a substituted aliphatic group...". An aliphatic group is defined in the specification page 17 lines 11 – 12 as:

> An aliphatic group is preferably a straight chained, branched or cyclic non-aromatic hydrocarbon...

Therefore there is antecedent basis for the term unsubstituted alkyl group in Claims 15 and 31. withdrawal of the rejection is respectfully requested.

The Examiner states that there is insufficient basis for the limitation "Y is a bond" in Claim 17. Claim 17 has been amended to remove this limitation.

The Examiner states that there is insufficient basis for the limitation "unsubstituted aryl group" in the definition of R_1 and R_2 in Claim 25 and "unsubstituted phenyl group" in the definition of R_1 and R_2 in Claim 28.

Claim 28 is dependent from Claim 27, which is dependent from Claim 26 which is dependent from Claim 25. Claim 25 is dependent from Claim 24 which is dependent from Claim 19 which in turn is dependent from Claim 18. In Claim 18 R_1 and R_2 are defined as:

...an aryl group or a substituted aryl group...

In this instance the duplication of the term aryl group in the definition of $R_1 - R_4$ was clearly intended to cover substituted and unsubstituted aryl groups. Consequently, Claim 18 has been amended to read "...an unsubstituted aryl group or a substituted aryl group...". This amendment is being made for clarification purposes, no narrowing of the claim is intended, nor is any new matter being added as a result of this amendment. Therefore, there is antecedent basis for the term unsubstituted aryl group in Claim 25.

A phenyl group is an aryl group and therefore there is antecedent basis for the term unsubstituted phenyl group in Claim 28. Withdrawal of the rejection is respectfully requested.

The Examiner states that there is insufficient basis for the limitation "unsubstituted aliphatic group" in the definition of R_3 and R_4 in Claim 25.

Claim 25 is dependent from Claim 24 which is dependent from Claim 18. In Claim 18 R_3 and R_4 are defined as:

...an aliphatic group or a substituted aliphatic group...

As discussed above Claim 18 has been amended to read "...an unsubstituted aliphatic group or a substituted aliphatic group...". Therefore Claim 25 is properly dependent and there is antecedent basis for all the terms described therein. Withdrawal of the rejection is respectfully requested.

Claim Rejection under 35 USC § 103 (a)

Claims 1-34 are rejected under 35 USC § 103(a) as being anticipated by Koya *et al.* 6,762,204, Koya *et al.* 6,800,660 and Koya *et al.* 6,924,312 in view of Calabresi et al., Goodman's and Gilman's.

The present application and Koya *et al.* 6,762,204, Koya *et al.* 6,800,660 and Koya *et al.* 6,924,312 were at the time the claimed invention was made, subject to obligation of assignment to the same Assignee. Copies of U.S Patents 6,762,204, 6,800,660 and 6,924,312 are being provided herewith. The Assignment information is shown on the face of these Patents, which demonstrates that all are assigned to Synta Pharmaceuticals Corp. A copy of the Assignment Document for the instant Application is also being provided herewith which shows that the inventors have assigned their rights in the instant Application to Synta Pharmaceuticals Corp.

In light of the above, the present application and Koya *et al.* 6,762,204, Koya *et al.* 6,800,660 and Koya *et al.* 6,924,312 were at the time the claimed invention was made, subject to obligation of assignment to the same Assignee.

In view of U.S.C. § 103 (c) (1) resulting from enactment of the American Inventors Protection Act (AIPA), the 6,762,204, 6,800,660 and 6,924,312 Patents would not be available as prior art under 102 (e)/103(a) against the present application as long as the filing date of the present application is on or after the date of enactment of the AIPA (November 29, 1999). As such, the 6,762,204, 6,800,660 and 6,924,312 Patents are disqualified as 102(e)/103 prior art under 35 U.S.C. § 103(c)(1). Therefore, Koya *et al.* 6,762,204, Koya *et al.* 6,800,660 and Koya *et al.* 6,924,312 do not preclude patentability of the instant claims. Withdrawal of the rejection is respectfully requested.

Claim Rejection under the judicially created doctrine of Double Patenting

The Examiner rejects Claims 1-17 and 30-34 under the judicially created of obviousness-type double patenting over Claims 1-3 of U.S. Patent No. 6,924,312.

The instant Claims 1-17 and 30-34 are directed to methods of treating multi-drug resistant cancers.

The claims of U.S. Patent No. 6,924,312 are directed to the use of the compounds described therein for treating cancer. The claims of U.S. Patent No. 6,924,312 do not teach treating multi-drug resistant cancers.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the compounds to subjects with drug-resistant cancers with the reasonable expectation that the compounds would demonstrate anti-cancer activity against the resistant cancer cells

Applicants respectfully disagree. The term "multi-drug resistant cancer" means that these cancers are resistant to treatment by cancer drugs. As such, cancer drugs which are known to be successful in treating cancer are not successful in treating these drug resistant cancers. Therefore, it would not have been expected at the time the invention was made that the compounds recited in the claims of U.S. Patent No. 6,924,312 would be successful in treating multi-drug resistant cancers. That is, it would not have been obvious to use a known cancer drug to treat a multi-drug resistant cancers, and further there would no reasonable expectation of success. Rather the opposite is true; the fact that a cancer is multi-drug resistant, one would typically expect that a cancer drug would not be effective, and would not demonstrate anti-cancer activity against the resistant cancer cells.

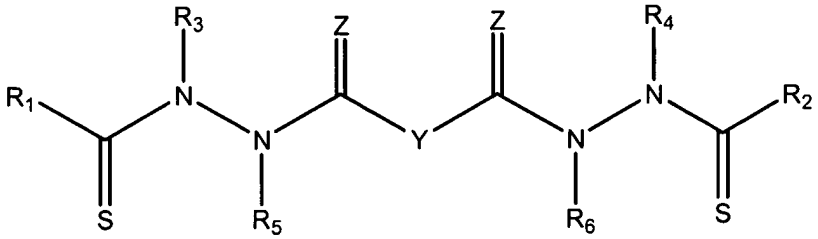
The Applicants' invention is non-obvious over the claims of U.S. Patent No. 6,924,312 because, *inter alia*, the degree of effectiveness of compounds in treating multi-drug resistant cancers shown in the subject application is unexpected. Specifically, Applicants have unexpectedly found that compounds **(1)** through **(18)** show much higher anti-cancer activity against **three distinct types** of multi-drug resistant cancers than commonly used anti-cancer drugs, such as, A taxol analog and Vincristine. Therefore, the present invention represents a surprising and unexpected improvement in therapies for multi-drug resistant cancers.

The claims of U.S. Patent No. 6,924,312 do not provide the expectation that compounds would have the effectiveness as shown, for example, in the *in vitro* studies in Examples 15 and 16. Accordingly, one of ordinary skill in the art would have no motivation to modify the claims of U.S. Patent No. 6,924,312 to obtain the invention of the instant claims, let alone a reasonable expectation that such a modification would be so successful. Therefore the instant claims are

unobvious and patentable in light of the claims of U.S. Patent No. 6,924,312. Withdrawal of the rejection is respectfully requested.

The Examiner also rejects Claims 18-29 and 35 under the judicially created of obviousness-type double patenting over Claims 78-117 of U.S. Patent No. 6,800, 660 and Claims 85-125 of U.S. Patent 6,762,204.

Claims 18-29 and 35 are directed to treatment of cancers comprising administering a compound represented by



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alone or in combination with a second anti-cancer agent other than a taxol analog.

The claims of U.S. Patent No. 6,800,660 and U.S. Patent No. 6,762,204 are directed to treating cancer in a subject comprising administering to the subject the compounds described therein **in combination with a taxol analog**.

The claims of U.S. Patent No. 6,800,660 and U.S. Patent 6,762,204 only teach the use of the recited compounds to enhance the anti-cancer activity of a taxol analog. The mechanism of how these compounds enhance the anti-cancer activity is not evident from the claims of either of U.S. Patent No. 6,800,660 or U.S. Patent 6,762,204. The claims of the U.S. Patent No. 6,800,660 and U.S. Patent 6,762,204 teach that the compounds recited therein somehow aid a taxol analog in killing cancer cells. However, it would not be obvious to assume that the compounds recited therein would possess anti-cancer activity. Because there is no teaching that the compounds would show any anti-cancer activity by themselves, it would not have been obvious to administer the compounds alone or in combination with any other anticancer drug to treat cancer, nor would there have been any reasonable expectation of success.

Applicants invention is non-obvious in light of U.S. Patent No. 6,800,660 and U.S. Patent No. 6,762,204 because the claims of U.S. Patent No. 6,800,660 and U.S. Patent No. 6,762,204 do not teach or suggest the use of the compounds described therein **alone** to treat cancer.

Applicants have discovered and demonstrated that compound **(1)** shows similar anti-cancer activity to commonly used anti-cancer drugs Vincristin and A taxol analog against seven different types of leukemia cell lines (Example 19) when administered alone. Further, Applicants have discovered and demonstrated that the compounds in the instant claims are effective in enhancing the anti-cancer of Epothilone D in treating human breast carcinoma in cell lines (Example 18).

The claims of U.S. Patent No. 6,800,660 and U.S. Patent No. 6,762,204 do not specifically disclose or otherwise suggest that the compounds could be used alone to treat cancer. Moreover, U.S. U.S. Patent No. 6,800,660 and U.S. Patent No. 6,762,204 do not provide the expectation that compounds would have the effectiveness as shown in Example 19. Accordingly, one of ordinary skill in the art would have no motivation to modify the claimed subject matter of U.S. Patent No. 6,800,660 and U.S. Patent No. 6,762,204 to obtain the invention of Claims 18-29 and 35, let alone a reasonable expectation that such a modification would be successful.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,
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